

**TRANSLATION**

**PATENT COOPERATION TREATY**

**PCT**

**INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY**

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference <b>36388P WO</b>	<b>FOR FURTHER ACTION</b>	See Form PCT/IPEA/416
International application No. <b>PCT/EP2006/008538</b>	International filing date ( <i>day/month/year</i> ) <b>31.08.2006</b>	Priority date ( <i>day/month/year</i> ) <b>01.09.2005</b>
International Patent Classification (IPC) or national classification and IPC <b>A61K47/48</b>		
Applicant <b>CELARES GMBH</b>		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of <u>9</u> sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising: a. <input checked="" type="checkbox"/> ( <i>sent to the applicant and to the International Bureau</i> ) a total of <u>24</u> sheets, as follows: <input checked="" type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions). <input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box. b. <input type="checkbox"/> ( <i>sent to the International Bureau only</i> ) a total of (indicate type and number of electronic carrier(s)) _____, containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items: <input checked="" type="checkbox"/> Box No. I Basis of the report <input type="checkbox"/> Box No. II Priority <input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability <input type="checkbox"/> Box No. IV Lack of unity of invention <input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement <input type="checkbox"/> Box No. VI Certain documents cited <input type="checkbox"/> Box No. VII Certain defects in the international application <input checked="" type="checkbox"/> Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
Name and mailing address of the IPEA/EP	Authorized officer
Facsimile No.	Telephone No.

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.

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## Box No. I Basis of the report

1. With regard to the language, this report is based on:

- ☒ the international application in the language in which it was filed
- ☐ the translation of the international application into \_\_\_\_\_, which is the language of a translation furnished for the purposes of:
- ☐ international search (Rule 12.3(a) and 23.1(b))
- ☐ publication of the international application (Rule 12.4(a))
- ☐ international preliminary examination (Rule 55.2(a) and/or 55.3(a))

2. With regard to the elements of the international application, this report is based on (replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):

- ☐ the international application as originally filed/furnished
- ☒ the description:
- pages 1-29 as originally filed/furnished
- pages\* \_\_\_\_\_ received by this Authority on \_\_\_\_\_
- pages\* \_\_\_\_\_ received by this Authority on \_\_\_\_\_
- ☒ the claims:
- nos. \_\_\_\_\_ as originally filed/furnished
- nos.\* \_\_\_\_\_ as amended (together with any statement) under Article 19
- nos.\* 1-22 received by this Authority on 02.07.2007 with letter of 02.07.2007
- nos.\* \_\_\_\_\_ received by this Authority on \_\_\_\_\_
- ☒ the drawings:
- sheets 1/26-5/26, 9/26, 10/26, 23/26-25/26 as originally filed/furnished
- sheets\* 6/26-8/26, 11/26-22/26, 26/26 received by this Authority on 02.07.2007 with letter of 02.07.2007
- sheets\* \_\_\_\_\_ received by this Authority on \_\_\_\_\_
- ☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages \_\_\_\_\_
- ☐ the claims, nos. \_\_\_\_\_
- ☐ the drawings, sheets/figs \_\_\_\_\_
- ☐ the sequence listing (specify): \_\_\_\_\_
- ☐ any table(s) related to sequence listing (specify): \_\_\_\_\_

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- ☐ the description, pages \_\_\_\_\_
- ☐ the claims, nos. \_\_\_\_\_
- ☐ the drawings, sheets/figs \_\_\_\_\_
- ☐ the sequence listing (specify): \_\_\_\_\_
- ☐ any table(s) related to sequence listing (specify): \_\_\_\_\_

\* If item 4 applies, some or all of those sheets may be marked "superseded."

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

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## Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims, Nos. 9 (in part)

because:

☐ the said international application, or said claims Nos. \_\_\_\_\_  
relate to the following subject matter which does not require an international preliminary examination (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 9 (in part)  
are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. \_\_\_\_\_ are so inadequately supported  
by the description that no meaningful opinion could be formed (*specify*):

☐ no international search report has been established for said claims Nos. \_\_\_\_\_

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b) and 13ter.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☒ See Supplemental Box for further details.

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Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement																					
1. Statement	<table><tbody><tr><td rowspan="2">Novelty (N)</td><td>Claims</td><td><u>1-22</u></td><td>YES</td></tr><tr><td>Claims</td><td></td><td>NO</td></tr><tr><td rowspan="2">Inventive step (IS)</td><td>Claims</td><td><u>1-8, 10-22</u></td><td>YES</td></tr><tr><td>Claims</td><td><u>9</u></td><td>NO</td></tr><tr><td rowspan="2">Industrial applicability (IA)</td><td>Claims</td><td><u>1-22</u></td><td>YES</td></tr><tr><td>Claims</td><td></td><td>NO</td></tr></tbody></table>	Novelty (N)	Claims	<u>1-22</u>	YES	Claims		NO	Inventive step (IS)	Claims	<u>1-8, 10-22</u>	YES	Claims	<u>9</u>	NO	Industrial applicability (IA)	Claims	<u>1-22</u>	YES	Claims		NO
Novelty (N)	Claims		<u>1-22</u>	YES																		
	Claims		NO																			
Inventive step (IS)	Claims	<u>1-8, 10-22</u>	YES																			
	Claims	<u>9</u>	NO																			
Industrial applicability (IA)	Claims	<u>1-22</u>	YES																			
	Claims		NO																			
2. Citations and explanations (Rule 70.7)	<p><b>D1:</b> WO 2004 083 258</p> <p><b>D2:</b> WO 98 184 94</p> <p><b>D3:</b> WO 02 43 772</p> <p><b>D4:</b> US 2003 0 161 791</p> <p><b>D5:</b> WO 2004 108 634.</p> <p><b>D1</b> are <b>D5</b> cited in the application.</p> <p><b>1.</b> <u>Amendments (PCT Article 33(2)(b))</u></p> <p>Compound (I) contains at least three groups of the formula (IIa) (original claim 1 and page 18), wherein T is TRIS-branched, as disclosed in the original claim 3 and on page 8. Dependent claims 3-22 have been brought into line. The drawings have been corrected since the claimed compounds contain no peroxy groups (PCT Rule 91.1). Thus, the requirements of PCT Article 33(2)(b) have been satisfied.</p> <p style="text-align: right;">/...</p>																					

Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
2.	<p data-bbox="412 401 894 432"><u>Novelty PCT Article 33(2)</u></p> <p data-bbox="412 506 1338 684">Compounds of the formula (I) with at least three polyalkylene oxide groups, wherein P is at least one of the three groups, are already known from the prior art:</p> <p data-bbox="412 716 1354 789"><b>D1</b> (page 29, second compound: see also page 28, lines 9-10; claims 3-4 and 23-24)</p> <p data-bbox="412 831 1354 957"><b>D2</b> (page 7, line 31 to page 8, line 1; page 9, lines 12-20 and 23-28; page 10, lines 11-26; example; claims 29, 33-34 and 40)</p> <p data-bbox="412 999 1370 1167"><b>D3</b> (page 9, line 16 to page 10, line 3; page 11, lines 3-6 and 14-17; page 16, line 17 to page 17, line 25: formulas Ib and Ic; example 6; claims 1, 4-5, 21, 25 and 28)</p> <p data-bbox="412 1209 1321 1283"><b>D4</b> (columns 48, 87, 93 and 119-122; claims 49 and 52-53)</p> <p data-bbox="412 1325 1321 1440"><b>D5</b> (example 3; example B; formula in C, in particular (XIIf), (XIIf), (XV) and (XVI); claims 1-2, 4 and 6).</p> <p data-bbox="412 1524 1370 1881">The known compounds are also used as reagents for modifying biopharmaceuticals (<b>D1</b>, columns 89-90, 139-141, claims 11 and 31; <b>D2</b>, page 2, lines 11-16 and 22-25; page 11, line 31 to page 12, line 13; claims 36 and 42; <b>D3</b>, page 22, lines 14-24; page 23, lines 17-21; page 27, line 1; claim 48; <b>D4</b>, columns 36, 67, 136 and 172; examples 5 and 7; claim 54; and <b>D5</b>, claims 9-15).</p>

Box No. V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Since, by contrast with claim 1 of the present application, the above compounds do not include any TRIS branching, novelty can be acknowledged in respect of the subject matter of claims 1-24.

3. Inventive step (PCT Article 33(3))

Prior art document **D5** also describes compounds of the formula (I) - with a total of at least three groups of the formula (IIa) but, by contrast with the disclosure of claim 1 of the present application, no TRIS-branched group T - as reagents for the modification of bio-pharmaceuticals. The problem addressed by the present application is that of devising a straightforward way of providing branched PEG reagents. The proposed solution lies in the provision of compounds that comprise three PEG groups (formula (IIa)) and a TRIS-branching group.

Known PEG reagents contain natural amino acids as branching components, said amino acids having known disadvantages (see the description, pages 3-6). Therefore even in D5, alternatives are sought. Although the compounds in D5 also contain at least three PEG groups of the formula (IIa) (D5, page 10), the branching T is a linear alkyl chain (D5, pages 18 and 22-23) or  $(\text{CO})\text{C}]_2(\text{C})(\text{CO})$  (D5: formula (XV) or (XVI)), and not  $\text{T} = \text{N}(\text{C})[\text{OCH}_2]_3$  as in the present application. The production of PEG reagents

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Box No. V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;  
citations and explanations supporting such statement

of up to 6 PEG chains was disclosed in D5. In the present application PEG reagents with a higher number of branches are produced using the TRIS branching group (see figures 20 and 21). Document D5 contains nothing to indicate that such a high degree of branching can be achieved by means of this type of synthesis.

Thus, the subject matter of claims 1-8 and 11-24 involves an inventive step. In the case of claim 9, the scope of protection is not clearly defined (see continuation of Box III in the Supplemental Box below).

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**Box No. VIII**      **Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The expression "preferably" is unclear since it has no restrictive effect on the scope of protection of the claim (see claim 13).



## Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Box III

**Box III: Non-establishment of opinion with regard to  
novelty, inventive step and industrial  
applicability**

Claim 9 relates to a specific compound (I). The scope of protection of said claim now appears to be broader than in the newly submitted claim 1 since P comprises two groups of the formula (II), not of the formula (IIa). Said compound should comprise three groups of the formula (IIa). This results in a lack of clarity (PCT Article 6).